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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PROUTY, REBECCA E	
ART UNIT	**PAPER NUMBER**
1652	20

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/884,889	Applicant(s) Robertson et al.
	Examiner Rebecca Prouty	Art Unit 1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 8, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *42-54 and 93-117* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *42-54 and 93-117* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 18
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 1-41 and 55-92 have been canceled. Claims 42-54 and newly presented claims 93-117 are still at issue and are present for examination.

Applicants' arguments filed on 8-8-03, paper No. 19, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 43-54, 93, and 108-117 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 93 (upon which Claims 43-54 depend) is indefinite in the recitation of "(d) a sequence to (a), (b), (c) or (d)" as it fails to recite the relationship of the sequence to the sequences of parts (a), (b) and (c) and it appears to depend from itself. It is assumed for purposes of examination that the instant phrase was intended to read "(d) a sequence complementary to (a), (b)or (c)"

Claims 108-117 are confusing in their dependence on Claim 97 (and ultimately on Claim 42) which recites methods of making variants of SEQ ID NO:7 yet further reciting increasing levels of identity to SEQ ID NO:5. Did applicants intend these claims to

depend from claim 93? This is assumed for purposes of further examination. Furthermore these claims are confusing in the recitation of "wherein the sequence" as it is unclear if "the sequence" refers to the sequence recited in part (a), (b), (c) or (d) of Claim 93.

Claims 42-54, 93 and 95-117 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a methods of using a genus of nucleic acid variants of either SEQ ID NOS:5 or 7. The specification does not contain any disclosure of the function of all nucleic acid variants of either SEQ ID NOS:5 or 7 used in the claimed methods. The genus of nucleic acids that comprise these above nucleic acid variants is a large variable genus with the potentiality of encoding many different proteins. Therefore, many functionally unrelated DNAs are encompassed within the scope of nucleic acids used in the methods of these claims. The specification discloses only a two species of nucleic acids to be used the claimed methods which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus.

Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 42-54, 93, and 95-117 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of generating a variant catalase comprising creating a library of variants of SEQ ID NO:5 or 7 by modifying (i.e., adding, deleting or substituting) one or more nucleotides of SEQ ID NOS:5 or 7, expressing said modified sequences, screening the proteins produced from said modified sequences for catalase activity and selecting a variant sequence which encodes a protein having catalase activity, does not reasonably provide enablement for methods of generating variants of SEQ ID NO:5 or 7 or variants thereof as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 42-54, 93, and 95-117 are so broad as to encompass methods of making any variant of SEQ ID NOS:5 or 7. The scope of

the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. While recombinant and mutagenesis techniques are known, the number of modifications that can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass methods of generating variants of the nucleic acids of SEQ ID NOS:5 or 7 or variants thereof because one of skill in the art would not know how to use the vast majority of the products of the claimed methods as the

specification does **not** establish: (A) regions of the protein structure which may be modified without effecting catalase activity; (B) the general tolerance of catalase genes to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including methods of making any variant of SEQ ID NOS:5 or 7 as the specification does not teach what one would use the vast numbers of variants which encode proteins lacking any catalase activity for and it is not predictable which modifications will lead to variants encoding active catalases. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of methods leading to genes having the desired biological characteristics is unpredictable and the experimentation left to those skilled in

the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim 94 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of generating a variant catalase comprising creating a library of variants of SEQ ID NO:5 or 7 by modifying (i.e., adding, deleting or substituting) one or more nucleotides of SEQ ID NOS:5 or 7, expressing said modified sequences, screening the proteins produced from said modified sequences for catalase activity and selecting a variant sequence which encodes a protein having catalase activity, does not reasonably provide enablement for methods of generating a variant catalase comprising modifying (i.e., adding, deleting or substituting) one or more nucleotides of SEQ ID NOS:5 or 7. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 94 is so broad as to encompass methods of generating a variant catalase comprising modifying (i.e., adding, deleting or substituting) one or more nucleotides of SEQ ID NOS:5 or 7. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods broadly encompassed by the claims. Since the

amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only two catalases.

While recombinant and mutagenesis techniques are known, there is no expectation in the art that any and all modifications of a sequence can be made without affecting the activity of the encoded protein as required by Claim 94, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. As such the skilled artisan would not expect the claimed methods to result in catalases at all absent a step of screening a group of variant

sequences for those which encode proteins which have catalytic activity. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including methods of generating a variant catalase comprising modifying (i.e., adding, deleting or substituting) one or more nucleotides of SEQ ID NOS:5 or 7.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 42, 43, 50, 93, 95, 96, and 108-112 are rejected under 35 U.S.C. 102(b) as being anticipated by Trakulnaleamsai et al. as evidenced by Loprasert et al. (reference AC of applicant's PTO-1449). The rejection is explained in the previous Office Action.

Applicants argue that Trakulnaleamsai et al. do not teach methods of mutating a nucleic acid having at least 50% identity to SEQ ID NO:7 or at least 65% identity to SEQ ID NO:5. This is not persuasive because the nucleic acid of Trakulnaleamsai et al. is 61% identical to SEQ ID NO:7 (and thus encompassed by all of Claims 42, 43, 50, 95 and 96) and Claims 93 and 108-112 do not

require the use of a nucleic acid at least 65% identity to SEQ ID NO:5. Claim 93 recites the use of any nucleic acid comprising a fragment of at least 30 consecutive nucleotides of a sequence having about 65% identity to SEQ ID NO:5. The nucleic acid of Trakulnaleamsai et al. comprises at least 2 regions of 33 nucleotides each having 91% identity to the corresponding portion of SEQ ID NO:5 (i.e., nucleotides 513-545 and 556-588 of Trakulnaleamsai et al are 91% identical to residues 459-491 and 502-534 of SEQ ID NO:5 respectively). This nucleic acid also anticipates Claims 108-112 which merely increase the level of identity required between the fragment and SEQ ID NO:5. However as noted Trakulnaleamsai et al. comprises at least 2 regions of 33 nucleotides each having 91% identity to the corresponding portion of SEQ ID NO:5 and thus anticipates these claims as well.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the

inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 42-53, 93, 95, 96, and 108-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trakulnaleamsai et al. in view of Short (US Patent 5,939,250). The rejection is explained in the previous Office Action.

Applicant has not presented any arguments specifically traversing this rejection but instead relies upon the traversal discussed above. Therefore, this rejection is maintained for the reasons presented above.

Claims 42, 43, 54, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trakulnaleamsai et al. in view of Short (US Patent 6,479,258). The rejection is explained in the previous Office Action.

Applicant has not presented any arguments specifically traversing this rejection but instead relies upon the traversal discussed above. Therefore, this rejection is maintained for the reasons presented above.

Claims 42-53, and 93-117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trakulnaleamsai et al. in view of Short (US Patent 5,939,250) and Robertson et al. (WO 98/00526).

Trakulnaleamsai et al. teach random mutagenesis of the *Bacillus stearothermophilus* catalase gene comprising isolating a 2.7 kb restriction fragment of the gene, chemically mutagenizing this fragment, reinserting it into an expression vector, and producing the mutant catalase. Trakulnaleamsai et al. do not teach the mutagenesis of other catalase genes.

Short teaches a number of known techniques for directed mutagenesis for the development of modified enzymes with particularly desired properties that are absent or less pronounced in the wild-type enzyme, such as stability to heat or organic solvents. Short specifically teaches "error-prone PCR", "shuffling", "oligonucleotide-directed mutagenesis", "assembly PCR", "sexual PCR mutagenesis", "in vivo mutagenesis", "cassette mutagenesis", "recursive ensemble mutagenesis", "exponential ensemble mutagenesis", and "site-specific mutagenesis".

Roberstson et al. teach the genes encoding the catalases of SEQ ID NOS:5 and 7. Robertson et al. do not teach methods of mutagenizing the genes of SEQ ID NOS: 5 and 7.

One of ordinary skill in the art at the time of filing would have been motivated to modify the nucleic acid sequence encoding the catalases of Roberstson et al. using each of the methods taught by Trakulnaleamsai et al. or Short, including "error-prone

PCR", "shuffling", "oligonucleotide-directed mutagenesis", "assembly PCR", "sexual PCR mutagenesis", "in vivo mutagenesis", "cassette mutagenesis", "recursive ensemble mutagenesis", "exponential ensemble mutagenesis", and "site-specific mutagenesis" in order to modify the amino acid sequence of the catalase such that the enzyme has a increased catalase activity or other particularly desired properties that are absent or less pronounced in the wild-type enzyme, such as stability to heat or organic solvents as taught by Short. One of ordinary skill in the art at the time of filing would have a reasonable expectation of success because of the high level of knowledge in the field of nucleic acid mutagenesis and the teachings of Trakulnaleamsai et al. who successfully generated a variant of the *Bacillus stearothermophilus* catalase encoding nucleic acid using similar mutagenesis methods.

Claims 42, 43, 54, 55 and 93-117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trakulnaleamsai et al. in view of Short (US Patent 6,479,258) and Robertson et al. (WO 98/00526).

Trakulnaleamsai et al. and Robertson et al. are discussed above. Trakulnaleamsai et al. do not use the methods of mutagenesis specifically recited in Claims 54 and 55 to produce

the mutant catalases. They further disclose that some of the catalase mutants had increased catalase and/or peroxidase enzymatic activity than the wild type protein.

Short teaches a number of known techniques for non-stochastic methods of directed mutagenesis for the development of modified enzymes with particularly desired properties that are absent or less pronounced in the wild-type enzyme, such as stability to heat or organic solvents. Short specifically teaches "gene reassembly", and "gene site saturated mutagenesis".

One of ordinary skill in the art at the time of filing would have been motivated to modify the nucleic acid sequence encoding the catalases of Roberstson et al. using each of the methods taught by Trakulnaleamsai et al. or Short, including "gene reassembly", and "gene site saturated mutagenesis" in order to modify the amino acid sequence of the catalase such that the enzyme has a increased catalase activity or other particularly desired properties that are absent or less pronounced in the wild-type enzyme, such as stability to heat or organic solvents as taught by Short. One of ordinary skill in the art at the time of filing would have a reasonable expectation of success because of the high level of knowledge in the field of nucleic acid mutagenesis and the teachings of Trakulnaleamsai et al. who

successfully generated a variant of the *Bacillus stearothermophilus* catalase encoding nucleic acid using similar mutagenesis methods.

It is noted that the Robertson et al. reference was published after the filing date of parent applications 08/951,844 and 08/674,887 to which applicants claim priority. However, the disclosure of the parent applications fails to disclose methods of mutagenesis of the disclosed catalase genes. As such the prior applications fail to provide support for the current claims and the instant application has been granted the benefit of the filing date only of the instant application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (703) 308-4000. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Rebecca Prouty
Primary Examiner
Art Unit 1652